Study synopsis.

EVALUATION OF THE EFFICACY AND SAFETY OF A THERMAL FRACTIONAL SKIN TREATMENT SYSTEM (TIXEL®) FOR THE TREATMENT OF FACIAL AND/OR SCALP ACTINIC KERATOSES

Study Protocol No:	**CLN 0827**
Revision:	**001**
Revision Date:	**Jan 16, 2022**
Investigational Product:	**Tixel Fractional System**
Sponsor:	**Novoxel Ltd.** **43 Hamelaha St.** **Poleg Ind. Zone, Netanya,** **Israel 4250573**
Contact:	**Ifat Klein, PhD** VP of Clinical Affairs ifat@novoxel.com **Raphi Shavit** Chairman, Novoxel Ltd. Raphi@novoxel.com

Study synopsis.

Study Synopsis

Protocol #	CLN 0827
Study Title	Evaluation of the Efficacy and Safety of a thermal fractional skin treatment system (Tixel®) for the treatment of facial and/or scalp actinic keratoses
Study Device	Tixel C (by Novoxel)
Device Description	Tixel technology is a thermal fractional skin treatment system powered by Thermo-Mechanical Action technology. Tixel employs a hot titanium tip which transfers direct heat to the skin. The proprietary tip is constructed of biocompatible temperature resistant titanium alloy cover mounted on gold plated copper base. The tip consists of an array of tiny pyramids which are heated to a temperature of 400°C. The apex of the pyramids transfers thermal energy to skin by very brief controlled contact time.
Study Design and Duration	Single-center, Prospective, Open Label, with Before-After Study Design. Up to 25 subjects will be enrolled to the study to provide at least 20 evaluable subjects. Subjects will be examined to determine the severity and extent of actinic keratoses. All subjects will undergo 1-3 treatments (determined by the investigator assessment), 3-4 weeks apart. Follow-up visits will be performed after the last treatment visit: 4 weeks (±7 days) and 12 weeks (±7 days). The inclusion criteria would be mild to moderate thickness confluent actinic keratoses located to scalp and/or face. Each subject will participate in the study for up to 20 weeks. Total study duration is estimated to be up to 12 months from enrollment of the first subject until last subject visit (including FUs).
Investigational Treatment	This is a non-invasive thermo-mechanical treatment to the scalp and/or face using the Tixel technology. The handpiece will be pressed gently onto the scalp/facial skin while transferring heat in a predetermined setting.
Objectives	**Primary objective** To evaluate the efficacy of the Tixel technology (device) for the treatment of facial and/or scalp actinic keratoses. **Secondary objectives** • To evaluate procedure-related adverse reactions. • To evaluate Subject's subjective downtime assessment. • To Evaluate the pain of the treatment. • To Evaluate the subject's satisfaction.

Study synopsis.

Study Population	Up to 25 subjects will be enrolled to the study to provide at least 20 evaluable subjects presenting with mild to moderate thickness confluent actinic keratoses located to scalp and/or face who wish to treat their condition by using a non-invasive thermo-mechanical treatment.
Inclusion Criteria:	1. Male and female, age 18-80 years old. 2. Skin Phototype I-VI. 3. Subject has mild to moderate thickness confluent AKs on his/her scalp and/or face. 4. Subject is willing and able to comply with protocol requirements and all study visits. 5. Subject has provided written informed consent.
Exclusion Criteria:	**General** 1. Any patient who has undergone tanning during the 4 weeks prior to any treatment session and/or any patient who plans to undergo tanning during the 4 weeks following any treatment session (patients who may be exposed to the sun for short periods of time occasionally are not contra-indicated as long as they apply a high SPF sunscreen (>50). 2. Current active Herpes Simplex infection. 3. Current skin cancer, malignant sites and/or advanced premalignant lesions or moles in the treatment area. 4. An impaired immune system condition or use of immunosuppressive medication. 5. Collagen disorders, keloid formation and/or abnormal wound healing. 6. Any patient who takes or has taken any medications (including via topical application), herbal treatment (oral or topic), food supplements or vitamins, which may cause fragile skin or impaired skin healing during the last 3 months. 7. Any patient who has used oral retinoids within 6 months prior to treatment or less. 8. Any patient who has a history of bleeding coagulopathies. 9. Any patient who has tattoos or permanent makeup in the treated area. 10. Any patient who has burned skin, blistered skin, irritated skin, or sensitive skin in any of the areas to be treated. 11. Women who are pregnant (as determined by self-reporting), lactating, or less than 3 months post-delivery, possibly pregnant or planning a pregnancy during the study period. 12. Currently participating in or recently participated in another clinical trial (within the last 30 days). **Previous/Current AKs Treatments** Subject underwent prior treatments for actinic keratoses including:

	13. Prior treatment with ablative laser, any laser or photo-dynamic therapy 3 months prior to enrollment. 14. Any cryotherapy or electrodessication 6 weeks prior to enrollment. 15. Systemic retinoid therapy within 6 months prior to enrollment, topical treatment with 5-Fluorouracil cream and/or imiquimod cream and/or diclofenac gel 6 months prior to enrollment. 16. Prior treatment with Tixel. **Treatment or treatment area related:** 17. Face cannot be treated due to dermal disorder other than AKs, such as infection, surgical treatment etc. **Medical Conditions** 18. Subject has a systemic disease manifested by AKs (e.g. immune suppression). 19. Significant systemic illness.
Study Evaluations	**Efficacy**: Lesion count by the investigator, confirmed and documented using Standardized high-resolution digital photography of the treatment area (before and after marking the present actinic keratoses using a washable eyeliner) will be performed for each subject at baseline (before), at each treatment visit (prior to the treatment session) and at 4 and 12 weeks FU visits. **Safety:** • Skin safety throughout the study as determined by the investigator on site before and after treatments as well as by examining the post-treatment occurrences of complications and adverse events. • Procedure related pain by VAS of 0-10 where a higher score indicates greater pain.
Primary Efficacy Endpoint:	The overall mean percentage reduction in actinic keratoses lesion count performed by the investigator manually, confirmed and documented using photograph images taken at baseline and at 12 weeks follow-up visit (or 12-weeks post last treatment if less than 3 treatments were done) (before and after marking the present actinic keratoses using a washable eyeliner) calculated as the relative change from baseline at 12 weeks. New lesions which were not existed in baseline will not be counted.
Secondary Efficacy Endpoints:	• The mean change in actinic keratoses lesion count, performed by the investigator manually, confirmed and documented using photograph images, from baseline at 4 and 12 weeks follow-up visit. • The overall mean percentage reduction in actinic keratoses lesion count performed by the investigator manually, confirmed and documented using photograph images taken at baseline and at 4 weeks follow-up visit (before and after marking the present actinic keratoses using a washable eyeliner) calculated as the relative change from baseline at 4

	weeks follow-up visit. New lesions which were not existed in baseline will not be counted. • Percentage of subjects that demonstrate a 26-50% in reduction in actinic keratoses lesion count 3 months after the final treatment. • Percentage of subjects that demonstrate a 51-75% in reduction in actinic keratoses lesion count 3 months after the final treatment. • Percentage of subjects that demonstrate more than 76% in reduction in actinic keratoses lesion count 3 months after the final treatment. • Subjects' satisfaction assessed at the final follow-up visit (based on the subject experience questionnaire which includes 3 questions relating to treatment results, treatment experience and treatment expectations) graded on a score of 1- 5; 1 being not satisfied and 5 being very satisfied).
Safety Endpoints	• Procedure related AEs • Subject subjective downtime assessment - defined as the period of time following the procedure during which the subject felt unable/unwilling to go out in public due to skin reactions. The assessment will be recorded by the subject using the Subject Subjective Downtime Assessment following each treatment and will be collected at the site at the follow-up visits up to 4weeks FU following treatment 3 (third treatment). • Procedure related pain by the subjects using VAS for pain of 0-10 where a higher score indicates greater pain.

Study Analysis Plan

Study Design and Objectives

This is a single-center, prospective, open label study with a before-after study design. The study is designed to evaluate the efficacy and safety of treating AKs of the scalp and/or face using the Tixel device.

Study Endpoints

Primary efficacy endpoint

The overall mean percentage reduction in AK lesion count performed by the investigator manually, confirmed and documented using photograph images taken at baseline and at 12 weeks follow-up visit (before and after marking the present actinic keratoses using a washable eyeliner) calculated as the relative change from baseline at 12 weeks. New lesions which were not existed in baseline will not be counted.

Secondary efficacy endpoints

- The mean change in actinic keratoses lesion count, performed by the investigator manually, confirmed and documented using photographic images, from baseline at 4 and 12 weeks follow-up visit.
- The overall mean percentage reduction in AK lesion count performed by the investigator manually, confirmed and documented using photograph images taken at baseline and at 4 weeks follow-up visit (before and after marking the present actinic keratoses using a washable eyeliner) calculated as the relative change from baseline at 4 weeks. New lesions which were not existed in baseline will not be counted

- Percentage of subjects that demonstrate a 26-50% in reduction in actinic keratoses lesion count 3 months after the final treatment.
- Percentage of subjects that demonstrate a 51-75% in reduction in actinic keratoses lesion count 3 months after the final treatment.
- Percentage of subjects that demonstrate more than 76% in reduction in actinic keratoses lesion count 3 months after the final treatment.
- Subject satisfaction assessment

Safety Endpoints

- Procedure related AEs

- Subject subjective downtime assessment - defined as the period of time following the procedure during which the subject felt unable/unwilling to go out in public due to skin reactions.

- Procedure related pain by the subjects using VAS for pain of 0-10 where a higher score indicates greater pain.

Study Hypothesis

In this study we will test the following hypothesis:

- Mean reduction in AKs lesion count 3 months after the final treatment will be at least 50%.

Sample Size Estimation

When the sample size is 20, a two-sided 95% confidence interval for a single mean will extend 8 from the observed mean, assuming that the standard deviation is known to be 20 and the confidence interval is based on the large sample z statistic.

If the expected rate is 58% the lower bound of the 95% confidence interval will be 50%.

A result of 58% will ensure with 95% level of confidence that the true percentage is not less than 50%.

REFERENCES :

Dixon, W.J., Massey, F.J. Introduction to Statistical Analysis. 4th Edition McGraw-Hill (1983) pp. 80-85

To overcome the expected dropout rate of up to 25% we will recruit up to 25 subjects.

Randomization and Blinding

Not relevant: Single arm non-randomized study. No blinding.

Full analysis set (FAS)

The full analysis set (FAS) includes all subjects who were enrolled and underwent at least one treatment with the study device.

Per-Protocol (PP)

The per-protocol analysis set (PP) will consist of only patients who received the full treatment session and have photos from the 3-month follow up visit.

Statistical Analysis of Analysis Sets

The FAS analysis set will serve as the main set for safety assessments. The primary efficacy assessment will be performed on the PP analysis set and as supportive analysis, on the FAS.

Statistical Analysis

General Considerations

Baseline demographic and other baseline characteristics, together with safety analyses will be performed on all enrolled subjects. Baseline values are defined as the last valid value prior to first treatment.

Statistical analyses of safety and secondary efficacy will be mainly descriptive in nature. Continuous variables will be summarized by a mean, standard deviation, minimum, 25th percentile median 75th percentile and maximum. Categorical variables by a count and percentage. Where confidence limits are appropriate, a two-sided 95% confidence interval will be constructed.

The required significance level of findings will be 5%. If statistical tests are performed, they will be two-sided and nominal *p*-values will be presented.

For comparison of means (continuous variables), the paired t-test or the Wilcoxon rank sum test will be used as appropriate. For comparison of proportions (categorical variables), the Chi-squared test or Fisher's exact test will be used as appropriate.

Analyses will be carried out using IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

Demographic and Other Baseline Variables

Demographic and baseline condition related characteristics will be tabulated. Continuous variables will be summarized by a mean, standard deviation, minimum, 25th percentile, median, 75th percentile and maximum, and categorical variables by a count and percentage.

Disposition of Subjects

The number of subjects screened and reasons for screening failures will be presented.

The numbers of subjects who were enrolled will be provided, as well as the reasons for all enrollment discontinuations, grouped by major reason (e.g., lost to follow-up, adverse event, etc.). A list of discontinued subjects, protocol deviations, and subjects excluded from the analyses will be provided as well.

Efficacy Analysis

Primary endpoint

The overall mean percentage reduction in AK lesion count performed by the investigator manually, confirmed and documented using photograph images taken at baseline and at 12 weeks follow-up visit calculated as the relative change from baseline at 12 weeks will be calculated along with 95% confidence interval.

The Paired T-test or Signed rank test for two means (paired observations) (as is appropriate) will be applied for testing the statistical significance of the percentage reduction in in actinic keratosis lesion count from baseline at week 12 (compared to 50%).

Secondary endpoints

- The mean change in in AK lesion count performed by the investigator manually, confirmed and documented using photograph images, from baseline at 4 and 12 weeks will be calculated along with 95% confidence interval.
  The Paired T-test or Signed rank test for two means (paired observations) (as is appropriate) will be applied for testing the statistical significance of the change in actinic keratosis lesion count from baseline at 4 and 12 weeks.

- The overall mean percentage reduction in AK lesion count performed by the investigator manually, confirmed and documented using photograph images taken at baseline and at 4 weeks follow-up visit calculated as the relative change from baseline at 4 weeks will be calculated along with 95% confidence interval.
  The Paired T-test or Signed rank test for two means (paired observations) (as is appropriate) will be applied for testing the statistical significance of the percentage reduction in in actinic keratosis lesion count from baseline at 4 weeks (compared to 50%).
- The percentage of subjects with lesion count reduction from baseline at 3 months between 26% and 50% will be calculated along with 95% exact confidence interval for proportions.
- The percentage of subjects with lesion count reduction from baseline at 3 months between 51% and 75% will be calculated along with 95% exact confidence interval for proportions.
- The percentage of subjects with lesion count reduction from baseline at 3 months higher than 76% will be calculated along with 95% exact confidence interval for proportions.
- The Subject satisfaction assessment score will be calculated along with 95% confidence interval.

Each of the above measures will be summarized by descriptive statistics by data type.

Safety Analysis

- Subject assessment of pain, as measured by a VAS score, associated with treatments will be tabulated and summarized *via* descriptive statistics.
- Skin safety throughout the study as determined by the investigator by examining the post-treatment occurrences of complications and adverse events.
- Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, most updated version) terminology and presented in tables by System Organ Class (SOC) and Preferred Term (PT).

- Adverse events (AE) will be presented by seriousness, severity, and relation to treatment.
- Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.

Pooling

Single center study not relevant.

Handling of Missing Data

Missing data will not be imputed.